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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/810,744	YOUNG ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *5-9,16-20 and 29-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-15 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/05 6/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed October 6, 2006 in response to the Office Action of September 6, 2006 is acknowledged and has been entered.

Applicant's election with traverse of Group I, claims 1-28 and the species (A2) non-conjugated antibodies, (C6) antibody mediates cytotoxicity through production of a conformational change in a cellular protein effective to produce a signal to initiate cell-killing, and (D1) murine antibody is acknowledged.

2. Applicants argue that claims 33-40 do not recite the phrase "selected from the group consisting of . . ." and thus are not presented in a Markush format.

This argument has been considered and is found persuasive.

3. Applicants argue that the inventions of Groups I, III and IV have the same objectives, method steps and criteria for success. Applicants argue that Group I is drawn to a method of treating a patient suffering from a cancerous disease by administering a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643. Applicants argue that Group III is drawn to a method of extending survival by treating a human tumor, i.e. cancerous disease, by administering a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643. Applicants argue that Group IV is drawn to a method of delaying disease progression by treating a human tumor, i.e. cancerous disease, by administering a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643. Applicants argue that thus, it is clear that the three groups have the same objective, i.e. treatment of cancerous disease, carried out by the same method, i.e. administration of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643.

4. Applicants argue that the treatment methods of Groups I, III and IV and the binding assay of Group II are each dependent upon the ability of the monoclonal antibody to interact with a MCSP antigenic moiety. Applicants argue that thus, Groups I-IV have the same criteria for success, i.e. the binding of the monoclonal antibody to a MCSP antigenic moiety.

Applicants' arguments have been carefully considered and are found persuasive, in part. Groups III and IV will be rejoined because extending survival and delaying disease progression are overlapping criteria for success because delaying disease progression would be expected to extend survival.

However, Groups I and Groups III/IV will remain separated for the reasons of record and the following reasons. Although applicants argue that Groups I and Groups III/IV have the same objective and method, the objective of Group III/IV is distinct from that of Group I in that Group III/IV is a method that requires extending survival and/or delaying disease progression and Group I does not. Additionally, Group I requires that the antibody of the method be characterized as being cytotoxic against cells of a cancerous tissue and Group III/IV does not have this limitation. Thus different searches and issues are involved in the examination of each Group and the literature search, particularly relevant in this art, is not coextensive.

Applicants argue that Group II and Groups I and III/IV are dependent on the ability of the monoclonal antibody to interact with a MCSP antigenic moiety. However, the success of the treatment methods of Groups I and III/IV depend not only on the antibody binding to its target antigen, but also on a host of other in vivo factors such as MCSP availability, the prevalence of MCSP on the target tissue, and non-specific binding of the antibody to other targets in vivo. Thus different searches and issues are involved in the examination of each Group and the literature

search, particularly relevant in this art, is not coextensive. Additionally, because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper

5. Applicants argue that the non-conjugated and conjugated antibodies are not independent inventions since conjugation is a further limitation on the antibody. Applicants argue conjugated antibodies comprise the same antibody as the non-conjugated antibodies (shared structure), which work by binding a MCSP antigenic moiety (shared mode of operation) to treat a cancerous disease (shared effects). Applicants argue a search for a non-conjugated antibody and the conjugated antibody clearly overlaps.

Upon review and reconsideration, given that the conjugation of antibodies to cytotoxicity enhancing compounds for enhanced efficacy in cancer treatment is well known in the art, the requirement for the election of species between an unconjugated and conjugated antibody will be vacated.

6. Applicants argue that the types of conjugates (toxins, enzymes, radioactive compounds and hematogenous cells) are presented in a Markush format. Applicants argue that the restriction of a Markush group is proper only where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility.

Applicants argue that the four types of conjugates disclosed share both a common utility, i.e. treatment of a cancerous disease, and a common structural feature, i.e. each type is

conjugated with the specific monoclonal antibody encoded by the clone deposited with the ATCC as PTA-5643. Applicants argue that utility of the treatment is dependent upon the binding of the monoclonal antibody to a MCSP antigenic moiety, i.e. the four types of conjugates share an antibody, which is essential to the utility as disclosed (treatment of cancerous disease). Applicants argue that a search for each of the four types of conjugates clearly overlaps.

This argument has been carefully considered, but has not been found persuasive. The members of the Markush Group do not share a structural feature that is essential to their utility. The antibody is not a structural feature of each member of this group. The utility of these conjugates is in their toxicity and the structurally required features for this utility are clearly distinct for toxins, enzymes, radioactive compounds and hematogenous cells. Additionally different searches and issues are involved in the examination of each conjugate and the literature search is not coextensive. Thus, the restriction of the Markush group is deemed proper.

However, the Markush group of conjugates will be rejoined given that conjugated and unconjugated antibodies have been rejoined for examination and in the interest of facilitating prosecution.

7. Applicants argue that all six types of cytotoxicity mediated by the described antibody are not independent inventions because each type places a further limitation on the antibody by defining how the cytotoxicity of the antibody is achieved. Applicants argue that all six types have the same effect, i.e. cytotoxicity. Applicants argue that a search of the prior art should center on the specific monoclonal antibody. Applicants argue that one of skill in the art would not attempt to search each of the six types of cytotoxicity mediated without connecting the

search to the antibody since a search of the six types alone would result with thousands of hits related to many different antibodies. Applicants argue that the search for types of cytotoxicity is considered overlapping and thus, the election of species is improper.

Applicants' argument has been considered, but has not been found persuasive because, for example, different antibody isotypes differ in their ability to stimulate complement-mediated cytotoxicity or antibody dependent cellular mediated cytotoxicity. Additionally, one of ordinary skill in the are would not predict that all antibodies, even those directed to the same antigen, would mediate all of the mechanisms of cytotoxicity claimed. For example not all antibodies have catalytic activity or can interfere with the function of the antigen they bind. Thus, the antibodies that effectively mediate each of theses forms of cytotoxicity are distinct and thus the literature search is not coextensive. Thus different searches and issues are involved in the examination of each species.

8. Applicants argue that that there are no human antibodies disclosed; the antibodies disclosed in the instant specification are murine antibodies and murine antibodies that have been humanized.

Upon review and reconsideration, the election of species between human and murine antibodies will be vacated.

The issues remain the same for the reasons set forth previously and above, thus the restriction requirement is deemed to be proper and is therefore made FINAL.

9. Claims 1-40 are pending.

10. Claims 5-9, 16-20, and 29-40 are hereby withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

11. Claims 1-4, 10-15, and 21-28 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-4, 10, 11, and 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 10, 11, and 23-28 are indefinite because claims 1 and 23 recite the phrase "identifying characteristics". The claims are indefinite because the specification provides no definition of "identifying characteristics". Thus it is not possible to determine if the identifying characteristics of the claimed product used in the claimed method are drawn to the product's characteristics as a monoclonal antibody, as a protein, as a binder to a particular antigen, or as a binder to a cancer cell. Given the above, the metes and bounds of the subject matter claimed cannot be determined and neither the specification nor the claims as originally filed particularly points out or distinctly claims the subject matter which applicant regards as the invention.

13. Claims 2, 4, 13, 15, 24, and 26 are indefinite because it recites the phrase a "chimerized antibody". The exact meaning of the word chimera is not known. The term chimera is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or

residues of human antibodies including but not limited to CDR grafted antibodies. Thus the metes and bounds of the claim protection sought cannot be determined.

14. Claims 1-4, 10-15, 21 and 22 are indefinite because claims 1 and 12 recite the phrase "essentially benign". The claims are indefinite because the specification provides no definition of "essentially benign". Thus it is not possible to determine what essentially benign is. For example, does essentially benign mean that the antibody is benign to a certain percentage of non-cancerous cells? If so, what percentage? Does essentially benign mean that the antibody affects all non-cancerous equally in some less than toxic manner? Given the above, the metes and bounds of the subject matter claimed cannot be determined and neither the specification nor the claims as originally filed particularly points out or distinctly claims the subject matter which applicant regards as the invention.

15. Claim 28 recites the limitation "humor tumor tissue sample" in claim 23. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a process for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface comprising: contacting said tumor cell with an isolated monoclonal antibody or antigen binding fragment thereof, said antibody or antigen binding fragment thereof being an isolated monoclonal antibody or antigen binding fragment thereof which binds to said expressed MCSP antigenic moiety, said antigenic moiety characterized as being bound by an antibody having the identifying characteristics of a monoclonal antibody encoded by the clone deposited with the ATCC as PTA-5643, whereby cell cytotoxicity occurs as a result of said binding.

The monoclonal antibody encoded by the clone deposited with the ATCC as PTA-5643, also referred to in the specification as 11BD-2E11-2, will be referred to as PTA-5643.

The specification teaches, based on mass spectroscopic identification combined with the confirmatory immunoprecipitation and western blotting experiments using known commercial antibodies, that the antigen for PTA-5643 is MCSP, see p. 39, lines 15-16 and Example 3.

The specification teaches that PTA-5643 was specifically cytotoxic in breast and ovarian cancer cells, and did not affect normal cells in *in vitro* assays, see p. 41, lines 15 and 16 and Table 2. The specification teaches that PTA-5643 had cytotoxic activity against the breast cancer cell line MCF-7, but not MDA-MB-468 or MDA-MB-231 breast cancer cells, see Table 2. The specification teaches that PTA-5643 had cytotoxic activity against the ovarian cancer cell line OVCAR-3, see Table 2.

The specification teaches that PTA-5643 displayed specific tumor binding to the breast tumor cell line MDA-MB-231, but not to the other breast cancer cell lines tested including MDA-MB-468 and MCF-7 (see Table 3), and several ovarian tumor cell lines including ES-2+SEAP (see Table 4). The specification teaches that there was also binding of PTA-5643 to non-cancer cells, however that binding did not produce cytotoxicity. The specification teaches that this was further evidence that binding was not necessarily predictive of the outcome of antibody ligation of its cognate antigen, and was a non-obvious finding. The specification teaches that this suggested that the context of antibody ligation in different cells was determinative of cytotoxicity rather than just antibody binding, see para. bridging p. 43 and 44.

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between contacting a cell with PTA-5643, the expression of MCSP, and the induction of cell cytotoxicity as a result of the binding PTA-5643. The specification teaches that in tumor cells that express MCSP, MDA-MB-231, PTA-5643 does not

have a cytotoxic effect. Furthermore, the specification teaches that PTA-5643 mediates cytotoxicity in tumor cells, MCF-7, that do not appear to express MCSP.

Thus, the given the above, one of ordinary skill in the art could not reasonably predictably identify an antibody that binds to MCSP that has the identifying characteristics of PTA-5643 that would mediate antibody cell cytotoxicity or predict that an antibody that binds to MCSP that has the identifying characteristics of PTA-5643 would mediate antibody cell cytotoxicity on a cell that expresses MCSP with a reasonable expectation of success without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

17. Claims 10 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method for treating a patient suffering from a cancerous disease in accordance with claims 1 or 12 wherein: the cytotoxicity of said antibody or fragment thereof is mediated through production of a conformational change in a cellular protein effective to produce a signal to initiate cell-killing.

The specification teaches that PTA-5643 was specifically cytotoxic in breast and ovarian cancer cells, and did not affect normal cells in *in vitro* assays, see p. 41, lines 15 and 16 and Table 2.

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between the cytotoxic activity of PTA-5643 and a conformational change in a cellular protein effective to produce a signal to initiate cell-killing. Neither the specification nor the art of record teach that PTA-5643 induces a conformational change in **any** protein. Additionally, neither the specification nor the art of record teach by what mechanism PTA-5643 induces cytotoxicity or whether induction of a conformational change in a cellular protein effective to produce a signal to initiate cell-killing is even an identifying characteristic of PTA-5643. Thus it is unclear from the information in the specification as originally filed and the art of record why applicant even suggests that PTA -5643 induces a conformational change in a cellular protein effective to produce a signal to initiate cell-killing. Given the above, one of ordinary skill in the art could not reliably predict that PTA -5643 or any antibody with identifying characteristics of PTA -5643 mediates its cytotoxic effect by inducing a conformational change in a cellular protein effective to produce a signal to initiate cell-killing. Thus undue experimentation would be required to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known

in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

18. If applicants were able to overcome the rejections set forth above claims 1-4, 10-15, and 21-27 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a patient suffering from **a breast or ovarian cancer** or for mediating cytotoxicity of **a breast or ovarian tumor cell** with a monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643, does not reasonably provide enablement for a method for treating a patient suffering from **a cancerous disease** or for mediating cytotoxicity of **a human tumor cell** with a monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method for treating a patient suffering from **a cancerous disease** or for mediating cytotoxicity of **a human tumor cell** with PTA-5643.

This means that one can treat a patient suffering from **any** cancerous disease or mediate cytotoxicity in **any** human tumor cells with PTA-5643.

The specification teaches that PTA-5643 was specifically cytotoxic in breast and ovarian cancer cells and no other cancer cell lines tested, and did not affect normal cells in *in vitro* assays, see p. 41, lines 15 and 16 and Table 2.

The specification teaches that when PTA-5643 was used for staining normal and breast cancer tissue, PTA-5643 staining was specific for cancerous, malignant breast cells, see p. 47 lines 5-8, Figure 8, and Table 6.

The specification teaches that the results of PTA-5643 cytotoxicity against MCF-7 and OVCAR-3 cells in culture was further extended by its anti-tumor activity towards these cancer cells when transplanted into mice (as disclosed in Ser. No. 10/762,129), see p.19, lines 5-7.

Furthermore, the specification teaches that PTA-5643 suppressed the growth of MDA-MB-468 tumors by 25 percent, see p.48 lines 20-22 and Figure 9. The specification teaches that although this was not a significant difference, a trend towards reduced tumor volume in comparison to the buffer control was observed throughout the study and therefore, PTA-5643 has shown efficacy in an established breast cancer model, para. p.48-49. The specification teaches that PTA-5643 reduced tumor burden and increased survival of mice bearing ES-2 ovarian tumors, see Example 8, para bridging p. 48-49, and Figs. 10 and 11.

One cannot extrapolate the teaching of the specification to the scope of the claims because the art teaches that PTA-5643 is selective for breast and ovarian cancer cells in its cytotoxic activity and the heterogeneity of cancers and their response to treatment is well known in the art.

1) In particular, as drawn to the heterogeneity of cancers, Young et al. (US Pat. No. 7,009,040 B2, 2003) teach that PTA-5643 (11BD-2E11-2) was specifically cytotoxic in breast and ovarian cancer cells, see column10 and Table 2. Furthermore, Young et al. teach that the antibodies were selective in their activity since not all cancer cell types were susceptible, see columns 10 and 11.

Furthermore, the art teaches that cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently.

Thus, it would not be predictably expected that a nexus, for example drawn to a connection between PTA-5643 and treating a patient suffering from a cancerous disease, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. Chemotherapy of Cancer; Second edition; John Wiley & Sons: New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between PTA-5643 and treating a patient suffering from a cancerous disease or mediating cytotoxicity of a human tumor cell in any tumor type other than breast and ovarian cancer, based on the information in the specification and known in the art without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the

art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

19. If applicants were able to overcome the rejections set forth above claims 1-4, 10, 11 and 23-28 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a patient suffering from a cancerous disease or for a process for mediating cytotoxicity with a monoclonal antibody or antigen binding fragment encoded by the cloned deposited with the ATCC as PTA-5643, does not reasonably provide

enablement for a method for treating a patient suffering from a cancerous disease or for a process for mediating cytotoxicity of a human tumor cell with a monoclonal antibody or antigen binding fragment **having the identifying characteristics** of a monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method for treating a patient suffering from a cancerous of a disease or for mediating cytotoxicity of a human tumor cell with a monoclonal antibody or antigen binding fragment **having the identifying characteristics** monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643.

This means that one can treat a patient suffering from a cancerous disease or mediate cytotoxicity in a human tumor cells **with any** monoclonal antibody or antigen binding fragment **having the identifying characteristics** monoclonal antibody encoded by the cloned deposited with the of ATCC as PTA-5643.

The specification teaches that PTA-5643 displayed specific tumor binding to the breast tumor cell line MDA-MB-231, but not to the other breast cancer cell lines tested including MDA-MB-468 and MCF-7, see Table 3. Additionally, the specification teaches that PTA-5643 had cytotoxic activity against the breast cancer cell line MCF-7, but not MDA-MB-468 or MDA-MB-231 breast cancer cells, see Table 2. The specification teaches that PTA-5643 has anti-tumor activity towards MCF-7 cancer cells when transplanted into mice (as disclosed in Ser. No. 10/762,129), see p.19, lines 5-7. Furthermore, the specification teaches that PTA-5643 suppressed the growth of MDA-MB-468 tumors by 25 percent, see p.48 lines 20-22 and Figure 9.

Although the specification teaches that PTA-5643 binds to MCSP, it does not define in the specification what the identifying characteristics of PTA-5643 are. Given that PTA-5643 displays cytotoxic activity and anti-tumor activity against cells in which MCSP appears not to be present, one of the identifying characteristics of PTA-5643 appears to be the binding of the antibody to an unknown antigen to mediate its cytotoxic and anti-tumorigenic effects.

One cannot extrapolate the teaching of the specification to the scope of the claims because there is insufficient guidance and direction as to how to make and use antibodies which **have the identifying characteristics** of monoclonal antibody PTA-5643 because no antibody, other than PTA-5643, has been shown to function as claimed and it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable.

In particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many

thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art in the absence of experimental evidence that any antibody (other than PTA-5643) with the undefined identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643 would function as claimed, no one skilled in the art would accept the assertion that any said antibodies are anti-cancer antibodies useful for cancer treatment or for a process of mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

20. If applicant were able to overcome the above rejections set forth above under 35 U.S.C. 112, first paragraph, claims 1, 3, 10-12, 14, 21, 23, 25, and 27 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a patient suffering from a cancerous disease or for a process for mediating cytotoxicity with a monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643, wherein said antibody is a **humanized** antibody, does not reasonably provide enablement for a method for treating a patient suffering from a cancerous disease or for a process for mediating cytotoxicity of a human tumor cell with a monoclonal antibody having the identifying characteristics of a monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643, wherein said antibody is a **murine** antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims read on treating a human tumor in a mammal with a mouse monoclonal antibody PTA-5643. This means the claims read on, and the specification contemplates, the treatment of cancer in humans with antibodies produced in a mouse.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

> the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The specification teaches that the monoclonal antibody PTA-5643 was obtained following immunization of mice with cells from a patient's breast tumor biopsy, para. bridging p. 18-19.

One cannot extrapolate the teachings of the specification to the scope of the claims because Winter et al (TIPS, 1993, 14:139-143) specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of human antimouse antibodies (HAMA) that can inactivate the injected antibodies. Thus, it would be expected that the injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. Further, Baselga et al (J. Clin. Oncol, 1996, 14:737-744) specifically teach that murine antibodies are limited clinically because they are immunogenic.

Given the above, it is clear that it is not possible to predict that a mouse monoclonal antibody PTA-5643 would successfully treat a human tumor in a human as contemplated in the

specification. Thus it would require undue experimentation to practice the broadly claimed invention.

21. If applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 3, 4, 14, 15, 25 and 26 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method for treating a patient suffering form a cancerous disease in accordance with claims 1 and/or 12 or a process for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface with antibody or antigen binding fragment there of having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643, wherein said isolated antibody or antigen binding fragments thereof are conjugated with a member selected from the group consisting of cytotoxic moieties, **cytotoxic enzymes**, radioactive compounds, and hematogenous cells, whereby an antibody conjugate is formed does not reasonably provide enablement for the method for treating a patient suffering form a cancerous disease in accordance with claims 1 and/or 12 or a process for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface with antibody or antigen binding fragment there of having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643, wherein said isolated antibody or antigen binding fragments thereof are conjugated with a member selected from the group consisting of cytotoxic moieties, **enzymes**, radioactive compounds, and hematogenous cells. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to the method for treating a patient suffering form a cancerous disease in accordance with claims 1 and/or 12 or a process for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface with antibody or antigen binding fragment there of having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643, wherein said isolated antibody or antigen binding fragments thereof are conjugated with a member selected from the group consisting of cytotoxic moieties, **enzymes**, radioactive compounds, and cytotoxic hematogenous cells.

This means that **any** of the listed compounds will be effective treating a patient suffering from a cancerous disease or for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface when conjugated to PTA-5643.

The specification teaches that Anti-MCSP antibodies have been conjugated to numerous toxic or chemotherapeutic agents, and these conjugates have demonstrated positive *in vivo* results when tested in murine models of melanoma, p. 22 lines 18-20.

One cannot extrapolate the teachings of the specification to the scope of the claims because not all enzymes (such as DNA polymerase)) have cytotoxic activity and it is well known in the art that cancer drug development is unpredictable.

In particular Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many

thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para).

Because of the known unpredictability of the art, in the absence of additional experimental evidence that any enzyme would treat a patient or have a cytotoxic towards a tumor cell when conjugated to PTA-5643, no one skilled in the art would believe it to be more likely than not that the broadly claimed antibody conjugates would function as claimed without undue experimentation.

21. Claims 1-4, 10, 11 and 23-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 10, 11 and 23-28 are broadly drawn to a method for treating a patient suffering from a cancerous of a disease or to a process for mediating cytotoxicity of a human tumor cell with a monoclonal antibody or antigen binding fragment **having the identifying characteristics** monoclonal antibody encoded by the cloned deposited with the ATCC as PTA-5643. It is noted that although the specification teaches that PTA-5643 binds to MCSP, it does not define in the specification what the identifying characteristics of PTA-5643 are. Given that PTA-5643 displays cytotoxic activity and anti-tumor activity against cells in which MCSP appears not to be present, one of the identifying characteristics of PTA-5643 appears to be the binding of the antibody to an unknown antigen to mediate its cytotoxic and anti-tumorigenic

effects. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a peptide antigen product itself logically cannot adequately describe an antibody to that antigen product.

Thus, the instant specification may provide an adequate written description of the antibody with identifying characteristics of PTA-5643 useful for treating a patient suffering from a cancerous disease or mediating cytotoxicity of a human tumor cell per Lilly by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus". Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe antibodies with identifying characteristics of PTA-5643 useful for treating a patient suffering from a cancerous disease or mediating cytotoxicity of a human tumor cell in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of the identifying characteristics of the claimed antibody, nor does the specification provide any partial structure of such identifying characteristics, nor any physical or chemical characteristics of the said identifying characteristics nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses that one of the PTA-5643 antigens is MSCP, the binding of MSCP does not appear to be required for the cytotoxic or anti-tumor function of PTA-5643. Thus this does not provide a description of the identifying characteristics of the claimed antibody.

The specification also fails to describe the identifying characteristics by the test set out in Lilly. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the claimed identifying characteristics of the monoclonal antibody PTA-5643 that are required to practice the claimed invention. Since the specification fails to adequately describe the identifying characteristics of the claimed antibodies useful for treating a patient suffering from a cancerous disease or mediating cytotoxicity of a human tumor cell, it also fails to adequately describe the claimed methods.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 25, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bumol et al. (PNAS, 1983, 80:529-533, IDS item).

Given the indefinite claim language drawn to "identifying characteristics" as set forth above, it is assumed for examination purposes that the identifying characteristics of the PTA-5643 include any monoclonal antibody which bind MCSP.

The specification teaches that the mAb 9.2.27 of Bumol et al. binds MSCP, see p. 3, lines 5-7.

The claims are drawn to a process for mediating cytotoxicity of a human tumor cell which expresses an MCSP antigenic moiety on the cell surface comprising: contacting said tumor cell with an isolated monoclonal antibody or antigen binding fragment thereof, said antibody or antigen binding fragment thereof being an isolated monoclonal antibody or antigen binding fragment thereof which binds to said expressed MCSP antigenic moiety, said antigenic moiety characterized as being bound by an antibody having the identifying characteristics of a monoclonal antibody encoded by the clone deposited with the ATCC as PTA-5643, whereby cell cytotoxicity occurs as a result of said binding (Claim 23), the process of claim 23 wherein said isolated antibody or antigen binding fragments thereof are conjugated with a member selected from the group consisting of cytotoxic moieties, enzymes, radioactive compounds, and hematogenous cells, whereby an antibody conjugate is formed (claim 25), and the process of

claim 23 wherein said isolated antibody or antigen binding fragments thereof are murine (claim 27).

Bumol et al. teach a murine, monoclonal antibody to MCSP (9.2.27) and conjugates of 9.2.27 to diptheria toxin A chain, see abstract and p. 529, both columns. Bumol et al. teach that 9.2.27 binds to the surface of melanoma cells, see p. 532, left column and Fig. 2A. Bumol et al teach that both 9.2.27 and the 9.2.27-conjugate decreased the volume of melanoma tumors implanted in athymic mice and suppressed established tumor growth, see p. 531-right column, p.532-left column, and Fig. 2. Bumol et al teach that both 9.2.27 and the 9.2.27-conjugate did not exhibit toxicity toward control lymphoblastoid cell lines in vitro, see p.531, right column.

Although Bumol et al. teach that 9.2.27 alone had variable toxic effects in *in vitro* assays (see p. 531-right column and Fig. 2B), the claims read on both *in vivo* and *in vitro* processes and the observed reduction in tumor volume indicates that 9.2.27 alone is cytotoxic *in vivo*. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bumol et al. (PNAS, 1983, 80:529-533, IDS item) as applied to claims 23, 25, and 27 above, in further view of Kimball (Introduction to Immunology, 3rd ed. Macmillan, Inc, New York,

1990, p. 507), in further view of Miller and Tannock (The Basic Science of Oncology, 2nd ed., McGraw- Hill Inc., 1992, Ch.14), and in further view of Riechmann et al (Nature Vol 332:323-327 1988).

The claims are drawn to a method for treating a patient suffering from a cancerous disease comprising: administering to said patient an anti-cancer antibody or fragment thereof produced in accordance with a method for the production of anti-cancer antibodies which are useful in treating a cancerous disease, said antibody or fragment thereof characterized as being cytotoxic against cells of a cancerous tissue, and being essentially benign to non-cancerous cells; wherein said antibody or fragment thereof is placed in admixture with a pharmaceutically acceptable adjuvant and is administered in an amount effective to mediate treatment of said cancerous disease; said antibody being an isolated monoclonal antibody or antigen binding fragment thereof which binds to an antigenic moiety expressed by said cancerous tissue, said antigenic moiety characterized as being bound by an antibody having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-5643 (claim 1), the method for treating a patient suffering from a cancerous disease in accordance with claim 1, wherein said isolated monoclonal antibody or antigen binding fragment thereof is humanized or chimerized (claim 2), the method for treating a patient suffering from a cancerous disease in accordance with claim 1 comprising: conjugating said antibody or antigen binding fragment thereof with a member selected from the group consisting of toxins, enzymes, radioactive compounds, and hematogenous cells, thereby forming an antibody conjugate; and administering said antibody conjugate or conjugated fragments to said patient; wherein said antibody conjugate or conjugated fragments are placed in admixture with a

pharmaceutically acceptable adjuvant and are administered in an amount effective to mediate treatment of said cancerous disease (Claim 3), the method of claim 3, wherein said antibody or fragment thereof is humanized or chimerized (claim 4), the process of claim 23 wherein said isolated antibody or antigen binding fragments thereof are humanized or chimerized (claim 24), The process of claim 25 wherein said isolated antibody or antigen binding fragments thereof are humanized or chimerized (claim 26).

Bumol et al. teach as set forth above.

Bumol et al. do not teach placing the antibody in an admixture with a pharmaceutically acceptable adjuvant or humanized/chimerized antibodies.

Kimball, page 507, teaches that adjuvants are material added to an antigen to increase its immunogenicity and adjuvants help stimulate immune responses to weakly immunogenic molecules, see p. 375.

Miller and Tannock teach that the nonspecific immunostimulant levamisole can lead to increased survival alone or when combined with the chemotherapeutic drug 5-fluorouracil in cancer patients, see p. 245, right column.

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human

pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Riechmann et al teach that the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facia* obvious to use both the antibody of claim 1 and an immunostimulatory adjuvant in combination for treating a patient suffering from a cancerous disease in view of the importance of eliminating cancer cells. Each of these agents had been taught by the prior art to be effective in treating a patient suffering from a cancerous disease, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to make a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant composition claimed, given the teaching of the prior art of compositions using either monoclonal antibodies with the identifying characteristics of PTA-5643 alone or conjugated to toxic agents or immunostimulatory adjuvants in the process in treating a patient suffering from a cancerous disease, it would have been obvious to treat a patient suffering from a cancerous disease with monoclonal antibodies with the identifying characteristics of PTA-5643 alone or conjugated to toxic agents in combination with immunostimulatory adjuvants because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for the same purpose

of treating a patient suffering from a cancerous disease. One of ordinary skill in the art would have reasonably expected to obtain effective treatment with either or both of these agents since both had been demonstrated in the prior art to be effective for treating a patient suffering from a cancerous disease.

Furthermore, as the level of ordinary skill in the immunology art is quite high, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to make humanized antibodies to the specificities taught by the prior art. One of ordinary skill in the art would have been motivated to make these antibodies in view of the fact that monoclonal antibodies to MCSP reduce tumor growth, see Bumol et al. citations above. Further, one of ordinary skill in the art would have been motivated to make humanized, monoclonal antibodies to MCSP with a reasonable expectation of success because Riechmann et al teach the advantage of using humanized antibodies to reduce immunogenicity.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

24. Claims 1-4, 10-15, and 21-27 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 10-15, and 21-27 of copending Application No.

10/949,846. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* , 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claim 28 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28 of copending Application No. 10/949,846.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. Claim 28 of Application No. 10/949,846 is drawn to the process of claim 23 wherein the human tumor tissue sample is obtained from a tumor originating in a tissue selected from the group consisting of breast, ovarian or melanoma tissue. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the

genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 1-4, 12-15, and 23-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-12, 15, 16 and 18 of copending Application No. 10/892,597.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the copending application and would have been obvious in view of the copending claims.

The instantly claimed method is generic to application number 10/892,597 which are drawn to a method of treating a human breast tumor in a mammal, comprising administering to said mammal the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-5643 or an antigen binding fragment produced from said isolated monoclonal antibody in an amount effective to reduce mammal's tumor burden (claim 10), the method of claim 10 wherein said isolated monoclonal antibody is conjugated to a cytotoxic moiety (claim 11), the method of claim 11 wherein said cytotoxic moiety is a radioactive isotope (claim 12), the method of claim 10 wherein the administered monoclonal antibody is a humanized antibody produced from the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-5643 (Claim 15), the method

of claim 10 wherein the administered monoclonal antibody is a chimeric antibody produced from the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-5643 (Claim 16). The method of claim 5 or claim 10 wherein binding of said isolated monoclonal antibody or said antigen binding fragment mediates cytotoxicity (claim 18).

Given that the claims of copending Application No. 10/892,597 are a species of the instantly claimed invention, they make obvious the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

27. Claims 1-4, 12-15, and 23-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-10 of copending Application No. 11/370,255.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the copending application and would have been obvious in view of the copending claims.

The instantly claimed method is generic to application number 11/370,255 which are drawn to a method for initiating antibody induced cellular cytotoxicity of cancerous cells in a tissue sample selected from a human breast or ovarian tumor comprising: providing a monoclonal antibody or cellular cytotoxicity inducing ligand in accordance with any one of claim 1 or 2 or 3, and contacting said monoclonal antibody or cellular cytotoxicity inducing

ligand with said tissue sample (claim 4), the monoclonal antibody or ligand of any one of claims 1, 2 or 3 conjugated with a member selected from the group consisting of cytotoxic moieties, enzymes, radioactive compounds, and hematogenous cells (claim 5), a method of treating human breast and ovarian tumors susceptible to antibody induced cellular cytotoxicity in a mammal, wherein said human breast and prostate tumors express an antigen which specifically binds to the isolated monoclonal antibody encoded by a clone deposited with the ATCC as accession number PTA-5643 or a cellular cytotoxicity inducing ligand thereof, comprising administering to said mammal a monoclonal antibody or cellular cytotoxicity inducing ligand in accordance with any one of claim 1 or 2 or 3, in an amount effective to induce cellular cytotoxicity and thereby reduce said mammal's tumor burden, (claim 6), the method of claim 6 wherein said monoclonal antibody or ligand is conjugated to a cytotoxic moiety (claim 7), the method of claim 7 wherein said cytotoxic moiety is a radioactive isotope (claim 8),

Given that the claims of copending Application No. 11/370,255 are a species of the instantly claimed invention, they make obvious the instantly claimed invention.

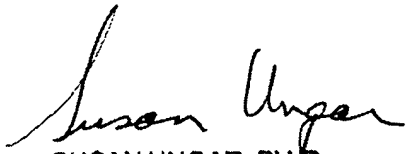
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. No claims are allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR